UNITED STATES DEPARTMENT OF COMMERCE
Patent and Trademark Office

Address : COMMISSIONER OF PATENTS AND TRADEMARKS
Washington, D.C. 20231

SERIAL NUMBER	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
08/012,269	02/01/93	KWON	B

ELLIS, J EXAMINER

18N1/0917

ART UNIT	PAPER NUMBER
1813	8

BARNARD & BROWN
200 EAST BUFFALO STREET
SUITE 102A
ITHACA, NY 14850

DATE MAILED: 09/17/93

This is a communication from the examiner in charge of your application
COMMISSIONER OF PATENTS AND TRADEMARKS

☒ This application has been examined ☒ Responsive to communication filed on 2/1/93 ☐ This action is made final.

A shortened statutory period for response to this action is set to expire 3 month(s), _____ days from the date of this letter.
Failure to respond within the period for response will cause the application to become abandoned. 35 U.S.C. 133

Part I THE FOLLOWING ATTACHMENT(S) ARE PART OF THIS ACTION:

1. ☐ Notice of References Cited by Examiner, PTO-892.
2. ☒ Notice re Patent Drawing, PTO-948.
3. ☒ Notice of Art Cited by Applicant, PTO-1449.
4. ☐ Notice of Informal Patent Application, Form PTO-152.
5. ☐ Information on How to Effect Drawing Changes, PTO-1474.
6. ☐ _____

Part II SUMMARY OF ACTION

1. ☒ Claims 1-21 are pending in the application.
   Of the above, claims 6-21 are withdrawn from consideration.
2. ☐ Claims _____ have been cancelled.
3. ☐ Claims _____ are allowed.
4. ☒ Claims 1-5 are rejected.
5. ☐ Claims _____ are objected to.
6. ☒ Claims 1-21 are subject to restriction or election requirement.
7. ☒ This application has been filed with informal drawings under 37 C.F.R. 1.85 which are acceptable for examination purposes.
8. ☐ Formal drawings are required in response to this Office action.
9. ☐ The corrected or substitute drawings have been received on _____. Under 37 C.F.R. 1.84 these drawings are ☐ acceptable. ☐ not acceptable (see explanation or Notice re Patent Drawing, PTO-948).
10. ☐ The proposed additional or substitute sheet(s) of drawings, filed on _____ has (have) been ☐ approved by the examiner. ☐ disapproved by the examiner (see explanation).
11. ☐ The proposed drawing correction, filed on _____, has been ☐ approved. ☐ disapproved (see explanation).
12. ☐ Acknowledgment is made of the claim for priority under U.S.C. 119. The certified copy has ☐ been received ☐ not been received ☐ been filed in parent application, serial no. _____; filed on _____
13. ☐ Since this application appears to be in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under Ex parte Quayle, 1935 C.D. 11; 453 O.G. 213.
14. ☐ Other

EXAMINER'S ACTION

Upon further consideration, the restriction requirement has been modified as set forth below to better reflect the nature of applicant's invention. The changes do not affect applicant's election of Group I.

Restriction to one of the following inventions is required under 35 U.S.C. § 121:

I. Claims 1-5, drawn to a DNA sequence, classified in Class 536, subclass 27.

II. Claims 6-8 and 17-20 drawn to a protein and a method of detecting cell membrane ligands classified in Class 530, subclass 350.

III. Claims 9-16, drawn to a monoclonal antibody, a hybridoma, and a method of enhancing T cell activation classified in Class 530, subclass 388.1.

IV. Claim 21, drawn to a method of inducing B cell proliferation, classified in Class 435, subclass 7.2.

The inventions are distinct, each from the other because of the following reasons:

Inventions I and II are related as process of making and product made. The inventions are distinct if either or both of the following can be shown: (1) that the process as claimed can be used to make other and materially different product or (2) that the product as claimed can be made by another and materially different process (M.P.E.P. § 806.05(f)). In the instant case the product as claimed can be made by a materially different process such as the Merrifield chemical synthesis technique.

Inventions II and III are related as product and process of use. The inventions can be shown to be distinct if either or both of the following can be shown: (1) the process for using the product as claimed can be practiced with another materially different product or (2) the

product as claimed can be used in a materially different process of using that product (M.P.E.P. § 806.05(h)). In the instant case the product as claimed can be used in a materially different process such as a reagent in a diagnostic assay.

The method of Groups II, III, and IV clearly differ in the method parameters, steps, and reagents used. The method of Group IV is directed to a method of inducing B-cell proliferation; whereas the methods of Groups II and III are directed to a method of enhancing T-cell activation and a method of detecting cell membrane ligands, respectively. These methods are independent and distinct from each other. Further, the method of Group IV does not require the products of Groups I-III.

Because these inventions are distinct for the reasons given above and have acquired a separate status in the art because of their recognized divergent subject matter restriction for examination purposes as indicated is proper.

During a telephone conversation with Mr. Michaels on September 13, 1993 a provisional election was made without traverse to prosecute the invention of Group I, claims 1-5. Affirmation of this election must be made by applicant in responding to this Office action. Claims 6-21 are withdrawn from further consideration by the Examiner, 37 C.F.R. § 1.142(b), as being drawn to a non-elected invention.

Applicant is reminded that upon the cancellation of claims to a non-elected invention, the inventorship must be amended in compliance with 37 C.F.R. § 1.48(b) if one or more of the currently named inventors is no longer an inventor of at least one claim remaining in the application. Any amendment of inventorship must be accompanied by a diligently-filed petition

under 37 C.F.R. § 1.48(b) and by the fee required under 37 C.F.R. § 1.17(h).

The specification is replete with grammatical errors too numerous to mention specifically. The specification should be revised carefully. Examples of such errors are: on p. 55 line 8, "minimal" is misspelled, line 22, "receptor" is misspelled, line 28, "mimicking" is misspelled, etc..

35 U.S.C. § 101 reads as follows:

> "Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter or any new and useful improvement thereof, may obtain a patent therefore, subject to the conditions and requirements of this title".

Claims 1-5 are rejected under 35 U.S.C. § 101 because lacks patentable utility.

The specification teaches the construction of cDNA libraries and the differential screening of said libraries in order to isolate nucleotide sequences which encode cytokines. The specification further discloses the isolation and characterization of a cDNA sequence known as 4-1BB. However, the specification fails to teach the biological activity of the protein encoded by Figure 2A. The specification teaches that the instant protein is constitutively expressed in both brain cells and renal medullar cells, and can be induced in heart and spleen cells. In addition, the protein has an amino acid sequence which is similar to tumor necrosis factor and nerve growth factor, as well as a consensus sequence which can bind protein tyrosine kinase, a zinc finger motif, a nuclear protein domain, and a receptor domain. In view of all the data, the specification proposes several roles for the 4-1BB protein such as a known or unknown

neurotrophic factor (p. 43, lines 8-9), an accessory signaling molecule during T cell activation (p. 43, line 26), a cell surface receptor for T cells (p. 55, lines 12-14), etc.; however, the actual function of the 4-1BB is not clear. Note that Chalupny et al., Proc. Natl. Acad. Sci. USA 89:10360 (1992) also teach that the function of 4-1BB is not known and the role of 4-1BB needs to be further characterized. See the abstract and p. 10364, last paragraph. In addition, Kwon et al., Cellular Immunology 121:414 (1989) teach that the nature of the 4-1BB gene product is difficult to predict. See p. 420, line 23. Furthermore, assuming arguendo that 4-1BB is a receptor protein, the specification fails to disclose the utility of a cDNA sequence which encodes an unknown receptor for an unknown ligand. Case law has established that the utility of an invention may not be based on mere assertion, but rather must be definite and in a currently available form. In Brenner V. Manson, 383 U.S. 519, 148 USPQ 689 (1966), the Supreme Court held:

> The basic quid pro quo contemplated by the Constitution and the Congress for granting a patent monopoly is the benefit derived by the public from an invention with substantial utility. Unless and until a process is refined and developed to this point- where specific benefit exists in currently available form- there is insufficient justification for permitting an applicant to engross what may prove to be a broad field.

The Court further stated:

> [t]hese arguments for and against the patentability of a process which either has no known use or is useful only in the sense that it may be an object of scientific research would apply equally to the patenting of the product produced by the process.

Applicants cannot rely on the fact that homologous nucleotide sequences encode polypeptides that possess a particular biological activity in order to establish a utility for the instant composition. See Brenner v. Manson at 694. In the instant case, the specification fails

to disclose a utility for the claimed compositions other than for further experimental purposes.

The following is a quotation of the first paragraph of 35 U.S.C. § 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

The specification is objected to under 35 U.S.C. § 112, first paragraph, as failing to provide an adequate written description of the invention and failing to provide an enabling disclosure.

The specification teaches the isolation and characterization of the nucleotide/amino acid sequence of the protein 4-1BB. However, the specification fails to provide an adequate written description, or teachings of enablement, of fragments and derivatives of the nucleotide sequence encoding 4-1BB which are capable of being used as a probe to isolate DNA sequences encoding proteins which are "similar" to the protein 4-1BB. First, the specification fails to provide an adequate written description as to what DNA sequences are to be isolated with the "probe". That is, the specification fails to disclose what constitutes a protein which is "similar" to the protein 4-1BB. Are proteins which share homology with the amino acid sequence of the instant protein similar? Proteins which have the same biological properties? Both? Or does applicant intend any nucleotide sequence which hybridizes under any experimental conditions? The mere hybridization of a "fragment" derived from the nucleotide sequence set forth in Figures 2A and 2B does not ensure the isolation of a known product with a known biological activity, especially

in view of the unknown biological role of the 4-1BB protein. The specification fails to teach whether protein 4-1BB is actually a receptor, and if so, whether it is a member of a family of receptor proteins, or what the degree of homology is among the family members. Accordingly, the specification fails to enable one skilled in the art to determine the hybridization conditions to employ for the identification and isolation of proteins which are "similar" to the instant protein. Second, the specification fails to provide an adequate written description, or a single working example, of nucleotide sequences which constitute a "derivative" of the 4-1BB nucleotide sequence. That is, the specification fails to provide an adequate written description, or teachings of enablement, as to the composition of 4-1BB "analogs". The specification fails to teach any methods of making a 4-1BB analog which has the same biological properties of the instant protein. In order to construct a biologically active analog, the specification must provide teachings as to what portions of the protein are essential for biological activity, and provide guidelines as to what alterations can be made to the amino acid sequence that would not affect its biological properties. The protein 4-1BB is approximately 250 amino acids in length, and there are 20 different amino acids which exist in nature. Accordingly, approximately 5,000 different 4-1BB analogs can be made by substituting only a single amino acid position, and over one million different analogs can be made by substituting three amino acids. It is well established that some amount of experimentation does not constitute a lack of enablement; however, the amount of experimentation must not be unduly extensive. See In re Fisher, 427 F.2d 833, 166 USPQ 18 (CCPA 1970). In the instant case, the specification fails to teach, or provide guidelines for, one skilled in the art to make biologically active analogs which are

effective as probes for "similar" proteins. Accordingly, one skilled in the art cannot make and use the invention as claimed. See Amgen v. Chugai Pharmaceutical Co. Ltd., 18 USPQ2d 1016 (Fed. Cir. 1991). Third, the specification fails to provide an adequate written description as to what regions of the 4-1BB sequences to employ as probes. Because it is not clear what nucleotide sequences are to be identified and isolated using fragments and "derivatives" of 4-1BB, it is not clear what regions of the instant cDNA to employ as a probe.

In addition, the specification fails to provide an adequate written description, or teachings of enablement, of the cDNA sequence which encodes the human receptor which "corresponds" to the mouse cDNA 4-1BB. First, the specification fails to teach the degree of homology between the mouse cDNA and the "corresponding" human cDNA. Absent this information, one skilled in the art cannot determine the hybridization conditions necessary in order to isolate a corresponding cDNA sequence encoding a human receptor protein. Second, the specification fails to teach the human tissue source which expresses the "corresponding" human receptor protein and which can be used to as a source of mRNA for the construction of a cDNA library. Accordingly, the specification fails to teach one skilled in the art how to make and use the claimed invention. In addition, the court has held that in order to satisfy the written description requirement of 35 USC §112, first paragraph, the specification must convey with reasonable clarity to those skilled in the art that as of the filing date sought applicant was in possession of the invention. See Vas-Cath Inc. v. Mahurkar, 19 USPQ2d 1111, 1117 (CAFC 1991). Further, "an adequate written description of a DNA requires more than a mere statement that it is part of the invention and reference to a potential method for isolating it; what is required is a

description of the DNA itself". See Fiers v. Sugano, 25 USPQ2d 1601, 1606. In the instant case the specification fails to provide an adequate written description of the claimed human cDNA sequence, a method of isolating said sequence, or the biological properties of the protein encoded by said sequence.

Claims 4 and 5 are rejected under 35 U.S.C. § 112, first paragraph, for the reasons set forth in the objection to the specification.

Claims 1-5 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 1-3 are inaccurate and misdescriptive in the recitation of a "cDNA gene". A gene is a region along a chromosome which codes for a functional product. A cDNA is not a region along a chromosome. Applicant appears to mean a "cDNA sequence which encodes...".

Claim 4 is vague and indefinite in the recitation of fragments and derivatives of the 4-1BB cDNA which can be used as probes. It is not clear which nucleotide sequences applicant intends. The claim is further vague and indefinite in the recitation of proteins which are "similar" to the receptor protein 4-1BB. It is not clear what nucleotide/amino acid sequences applicant intends.

Claim 5 is vague and indefinite in the recitation of the "cDNA of a human receptor corresponding to the mouse cDNA 4-1BB". It is not clear what cDNA sequence(s) applicant intends. The claim is further vague and indefinite in the recitation of a "human source". It is

not clear what "source" applicant intends.

The following is a quotation of 35 U.S.C. § 103 which forms the basis for all obviousness rejections set forth in this Office action:

> A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.
>
> Subject matter developed by another person, which qualifies as prior art only under subsection (f) or (g) of section 102 of this title, shall not preclude patentability under this section where the subject matter and the claimed invention were, at the time the invention was made, owned by the same person or subject to an obligation of assignment to the same person.

Claims 1-5 are rejected under 35 U.S.C. § 103 as being unpatentable over Kwon et al., Proc. Natl. Acad. Sci. USA 84:2896 (1987) in view of Maniatis et al..

Kwon et al. teach the isolation and identification of several cDNA clones which encode lymphokines. Kwon et al. teach both the construction of a cDNA library from specific cell lines and a method of differential screening to isolate cDNA sequences encoding lymphokines. Kwon et al. do not disclose the nucleotide sequences of said cDNA clones. Note Table 2, L3G29#4 encodes a region of the 4-1BB nucleotide sequence. Maniatis et al. teach the standard techniques in molecular biology for isolating and sequencing the complete nucleotide sequence of an isolated DNA fragment. Accordingly, in view of the teachings of Kwon et al. as to the method of constructing a cDNA library and isolating a cDNA clone encoding 4-1BB, and the teachings of Maniatis et al. as to the standard methods in recombinant DNA technology for determining the

nucleotide sequence of an isolated cDNA clone, and absent unexpected results, it would have been obvious to one of ordinary skill in the art to determine the nucleotide sequence of the full-length L3G29#44 (4-1BB) cDNA clone. It would have been obvious to employ known materials for their known and expected properties.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to J. Ellis whose telephone number is (703) 308-3990.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (703) 308-0196.

J. Ellis, Ph.D.
September 14, 1993

JOAN ELLIS
PRIMARY EXAMINER
GROUP 180